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Cardiac safety of second-generation H_1-antihistamines when updosed in chronic spontaneous urticaria

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Abstract

The symptoms of chronic urticaria, be it chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CindU), are mediated primarily by the actions of histamine on H_1 receptors located on endothelial cells (the weal) and on sensory nerves (neurogenic flare and pruritus). Thus, second-generation H_1 antihistamines (sgAHs) are the primary treatment of these conditions. However, many patients are poorly responsive to licensed doses of antihistamines. In these patients, the current EAACI/GA^{2}LEN/EDF/WAO guideline for urticaria suggests updosing of sgAHs up to fourfold. However, such updosing is off-label and the responsibility resides with the prescribing physician. Therefore, the safety of the drug when used above its licensed dose is of paramount importance. An important aspect of safety is potential cardiotoxicity. This problem was initially identified some 20 years ago with cardiotoxic deaths occurring with astemizole and terfenadine, two early sgAHs. In this review, we discuss the mechanisms and assessments of potential cardiotoxicity of H_1 antihistamines when updosed to four times their licensed dose. In particular, we have focused on the potential of H_1 antihistamines to block hERG (human Ether-a-go-go-Related Gene) voltage-gated K^+ channels, also known as Kv11.1 channels according to the IUPHAR classification. Blockade of these channels causes QT prolongation leading to torsade de pointes that may possibly degenerate into ventricular fibrillation and sudden death. We considered in detail bilastine, cetirizine, levocetirizine, ebastine, fexofenadine, loratadine, desloratadine, mizolastine and rupatadine and concluded that all these drugs have an excellent safety profile with no evidence of cardiotoxicity even when updosed up to four times their standard licensed dose, provided that the prescribers carefully consider and rule out potential risk factors for cardiotoxicity, such as the presence of inherited long QT syndrome, older age, cardiovascular disorders, hypokalemia and hypomagnesemia, or the use of drugs that either have direct QT prolonging effects or inhibit sgAH metabolism.

KEYWORDS

cardiovascular safety, long QT syndrome, pharmacology and pharmacogenomics, second generation antihistamines, torsades de points, urticaria

Taglialatela and Church shared last authorship

1 | INTRODUCTION

The symptoms of chronic urticaria, be it chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CindU), are mediated primarily by the actions of histamine on H_1 receptors located on endothelial cells (the weal) and on sensory nerves (neurogenic flare and pruritus). The burden of CSU, which is defined as the spontaneous appearance of signs and symptoms of urticaria for more than 6 weeks,[1] is substantial for patients, their family and friends, the healthcare system and society. Continuous treatment with second-generation H_1 antihistamines (sgAHs) is of eminent importance in the treatment of patients with CSU. However, many patients are poorly responsive to licensed doses of antihistamines. In these patients, the current EAACI / GA^{2}LEN/EDF/WAO guideline for urticaria suggests updosing of sgAHs up to fourfold.[1] However, such updosing is off-label, and consequently, the responsibility resides with the prescribing physician. In this case, the safety of the drug when used above its licensed dose is of paramount importance. This issue is of unquestionable clinical relevance, considering that astemizole and terfenadine, two of the first marketed sgAHs, have been linked to one of the most serious cases of unexpected toxicity after marketing approval: delayed ventricular repolarization (QT interval prolongation) leading to torsade de pointes (TdP) possibly degenerating into ventricular fibrillation and causing sudden death.[2-6]

Over 15 years have lapsed since the cardiotoxicity of sgAHs was reviewed in a consensus paper,[7] which did not, however, specifically address the updosing issue. Therefore, in this manuscript, we have re-addressed the mechanisms for potential cardiotoxicity of antihistamines, summarized the tests used to investigate this and reviewed the cardiac safety profiles of 9 sgAHs used in the treatment of chronic urticaria. We hope that this will eliminate the nagging doubt about the potential of cardiotoxicity with updosing with an H_1 antihistamine in the treatment of patients with chronic spontaneous urticaria.

2 | MECHANISMS AND ASSESSMENTS OF CARDIOTOXICITY OF H_1 ANTIHISTAMINES

The mechanism most frequently involved in cardiotoxicity induced by sgAHs is the blockade of hERG (human Ether-a-go-go-Related Gene, Kv11.1) voltage-gated K^+ channels (Figure 1). These channels contribute to cardiac repolarization by carrying the I_{Kr} current and, therefore, their blockade causes QT prolongation and ultimately torsade de pointes.[8-13] The molecular determinants for histamine H_1 receptor and hERG channel affinities are completely unrelated for both, first-generation AHs[12] and sgAHs (Figure 1).[9] For most H_1 antihistamines, the plasma concentrations for antihistaminic activity are much lower than those required for hERG channel activation, and only when they are similar is there an enhanced risk of a problem. On this conceptual basis, it has been proposed that the ratio between the hERG IC_{50} (ie the concentration of drug that causes a 50% decrease in the current carried by hERG channels) and the antihistaminic response EC_{50} (ie the concentration of drug that causes the 50% of the desired anti-allergic effect) could be used as an indicator of the arrhythmogenic potential of sgAHs, defining a so-called cardiac safety index (CSI).[14] Specific problems arise, however, when trying to define CSI threshold levels below which a drug has to be considered as potentially dangerous. Cavero et al[14] suggested that the CSI threshold should be set at 30, although additional factors contributing to a more complete definition of the risk/benefit ratio for each 2ndGAH should be also taken into account. In support of this view, Redfern and co-workers highlighted that the CSI for the cardiotoxic sgAHs terfenadine and astemizole, calculated as the ratio between hERG IC_{50} and the effective drug therapeutic plasma concentration (ETPC), was < 30, while > 30 values are reported for safer sgAHs such as cetirizine, loratadine, mizolastine, ebastine and fexofenadine.[15] Values of CSI > 30 times the threshold are a strong argument in support of the cardiovascular safety of antihistamine updosing

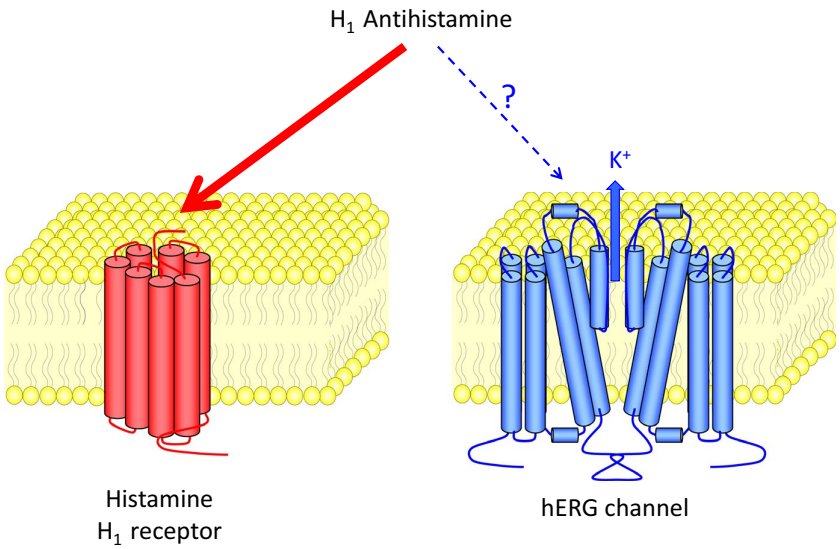

FIGURE 1 Diagrammatic representation of the histamine H_1 receptor and the hERG channel in biological membranes. Structurally the binding sites have completely different structures. While H_1 antihistamines have strong binding to histamine H_1 receptors, a different part of the molecule has very weak or negligible binding to the hERG channel. Consequently, potential cardiotoxicity is not a class effect

considering that all drugs belonging to this class have linear and largely predictable pharmacokinetics and that plasma concentrations are roughly expected to increase proportionally when the drug is updosed. Most sgAHs are tightly bound to plasma proteins and display rather low distribution volumes.[16] Therefore, given that only the free drug fraction is available to interact with hERG channels and that, in most cases, therapeutic drug monitoring does not discriminate between free and bound fractions, it seems reasonable to assume that the drug concentration effectively available to block hERG will be much lower than the total plasma concentration;[16] as a matter of fact, the unbound ETPC was used by Redfern[15] to calculate CSI.

While these considerations predict sgAH updosing to be generally safe, doctors need to be particularly aware of the risk factors known to precipitate arrhythmic episodes observed at recommended doses of sgAHs; these include concomitant use of QT prolonging drugs and of drugs that can disproportionally increase the plasma concentrations of sgAHs by pharmacokinetic interactions, electrolyte unbalances such as hypokalemia or hypomagnesemia, previous cardiac dysfunction and congenital long QT syndrome.

The identification of hERG as a specific molecular target for drug-induced proarrhythmic effects has led to several attempts to standardize the preclinical assessment of the IC_{50} for hERG block, as summarized in the S7B ICH Harmonised Tripartite Guideline on the "Non clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals."[17] This document was then followed and complemented by the ICH E14 Guideline entitled "The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non anti-arrhythmic drugs," defining the characteristic of the so-called thorough QT (TQT) study, which represents the reference protocol for drug proarrhythmic risk assessment for regulatory purposes using a 12-lead ECG recording.[18] Briefly, in a typical TQT study, the QT interval is corrected for heart rate with specific formulas such as the Fridericia's correction; moreover, a positive control represented by a drug unequivocally proven to prolong QTc is always included, and candidate drugs are investigated not only at the recommended therapeutic dose but also at higher doses (usually threefold), a critical issue for our updosing perspective. The ICH E14 Guideline was first issued in 2004 (thus after the publication of our previous consensus paper[7]). Therefore, no TQT studies were performed with sgAH drugs licensed before that date. At the time of writing, only bilastine, levocetirizine and rupatadine have been investigated in formal TQT studies.[19-22] For all other sgAHs, non-ICH E14 compliant data are available, which, however, often includes doses larger than those recommended.

3 | CARDIAC SAFETY OF SGAHS USED AT HIGHER THAN STANDARD DOSES

The next paragraphs summarize relevant preclinical (hERG blockade) and clinical (plasma concentration values, TQT/ conventional ECG studies) information regarding the cardiovascular safety of specific sgAHs, with special reference to updosing issues (Table 1).

3.1 | Bilastine

The recommended dose of the benzimidazole-piperidine sgAH bilastine is 20 mg/day.[23,24] This drug has optimal pharmacological properties for updosing including a high selectivity for H_1 receptors, the lack of a significant CYP450-mediated metabolism and the predicted poor retention in the brain being a good substrate for P-glycoprotein-mediated transport.[25] Importantly, updosing is also expected not to impact significantly on cardiovascular risk. Indeed, the IC_{50} for hERG blockade in vitro is between 6500 and 17 170 nM,[23] whereas C_{max} at steady state was about 2-10 times lower in patients treated with single or repeated doses of 20 and 100 mg/day[22] (Table 1). A formal TQT study confirmed the lack of significant effects on cardiac repolarization of bilastine doses fivefold higher than those recommended.[20,22] The clinical evidence accumulated so far confirms the safety of bilastine updosing in patients with cold urticaria,[26] chronic spontaneous urticaria[27] and pruritus.[28]

3.2 | Cetirizine and levocetirizine

Cetirizine, the carboxylated metabolite of hydroxyzine, is a sgAH of the piperazine family with very low sedating and anticholinergic activities.[29] Cetirizine has a chiral centre and, therefore, exists in two enantiomeric forms, R- and L-cetirizine, of which only L-cetirizine (levocetirizine) is active on H_1 receptors. Levocetirizine has a similar tolerability and a higher potency than the parent racemic form, cetirizine.[30-32]

The recommended daily dose of cetirizine and levocetirizine is 10 and 5 mg/day, respectively.[33,34]

Both cetirizine and levocetirizine have been successfully and safely updosed for the treatment of cholinergic and chronic spontaneous urticaria.[35-43] Both drugs appear remarkably safe from a cardiovascular point of view, and they are well suited for updosing. Cetirizine is inactive on hERG channels in concentrations up to 3000 nM in mammalian cells.[44,45] This is higher than the C_{max} attained after a single or repeated administration at doses up to threefold higher than the recommended one[30,46] (Table 1). Concerning levocetirizine, no effect on cloned hERG channels was observed in Xenopus oocytes at concentrations up to 30 000 nM.[47] This drug reaches peak plasma concentrations of <1000 nM after single or repeated administrations of the recommended 5 mg dose, whereas few data are available on the higher doses (Table 1). Remarkably, however, a C_{max} value of about 3000 nM was recorded in volunteers taking a single sixfold higher dose of 30 mg.[21] Collectively, these data argue against a significant blockade of hERG channels in vivo by cetirizine and levocetirizine. In agreement with this, cetirizine did not prolong the QTc interval at doses of up to 60 mg/day (six times the recommended dose) in a non-TQT study performed before the publication of the (ICH) E14 guidance.[48] The safety of levocetirizine

TABLE 1 Selected pharmacodynamic and pharmacokinetic parameters of the sgAHs mentioned in the text

	hERG IC_{50}[a] (nM)	H1 receptor K_i[b] (nM)	Protein binding (%)		C_{max} standard dose (nM)	C_{max} Updosing (nM)
BILASTINE	6500-17170[23]	64[105]	84-90[23]	Single dose	490[106]	Fivefold: 3407[106]
				Repeated doses	449[22]	Fivefold: 3041[22]
CETIRIZINE	No effect up to 3000[44,45]	47[107]	93[33]	Single dose	550[46]	Threefold: 1740[46]
				Repeated doses	799[46]	Threefold: 2140[46]
DESLORATADINE	1950[74]	0.9[107]	82-87[108]	Single dose	7.0[76]	Fourfold: 26.0[76]
				Repeated doses	12.8[109]	Ninefold: 161.2[65]
EBASTINE[c]	Ebastine: 300[51] carebastine: na- possibly inactive (see text)	Ebastine :52[107] carebastine: 10[107]	Carebastine: 98[50]	Single dose	220[53]	Threefold: 440[53]
						Fourfold: 620[53]
						Fivefold: 861[53]
				Repeated doses	260-320[110]	Twofold: 793[111]
FEXOFENADINE	214000[57]	175[107]	60-80[112]	Single dose	60 mg: 283[112]	Threefold (2.7)[c]: 6494[58]
					180 mg: 358[112]	Fourfold (4.4)[c]: 12723[58]
				Repeated doses	60 mg bid: 596[112]	Threefold (2.9)[c]: 3124[58]
						Eightfold (7.6)[c]: 9323[58]
LEVOCETIRIZINE	No effect up to 30000[47]	3[113]	91-92[34]	Single dose	586[21]	Sixfold: 3348[21]
				Repeated doses	792[34]	na
LORATADINE	101000[45] 5150[74]	138[107]	97-99[75]	Single dose	5.5[75]	Fourfold[d]: 68.3[75]
					12.3[d75]	
				Repeated doses	12.1[81]	na
MIZOLASTINE	350[88]	22[107]	98.4[114]	Single dose	527[89]	Fourfold: 2268[89]
				Repeated doses	539[89]	Fourfold: 2446[89]
RUPATADINE	8100[94]	3.8[115]	98-99[115]	Single dose	6.3[96]	Tenfold: 38.5[96]
				Repeated doses	7.45[96]	Tenfold: 552.9[96]

[a]IC_{50} stands for the half maximal inhibitory concentration, that is the concentration of a given drug that causes a 50% inhibition of a specific biological or biochemical activity. In the specific case of sgAHs and hERG activity, it indicates the concentration of the antihistamine drug needed to cause a 50% decrease in the amplitude of the K^+ currents carried by these channels in electrophysiological experiments in vitro.
[b]K_i is the inhibitory constant and measures the affinity of a certain drug inhibitor for its target; in the specific case reported in this table, it measures the affinity of the indicated sgAHs for H1 receptors in binding experiments in vitro. It is important to mention here that K_i and binding IC_{50} are not identical because the latter but not the former depend on the experimental condition (eg on the concentration of the target protein). For competitive agonists and antagonists, K_i can be obtained from IC_{50} data by using the Cheng and Prusoff equation.[116]
[c]Fexofenadine doses used in ref.[57] are not exact multiples of the therapeutic doses. The closest values to the upscaled doses have been reported, and the exact ratios to therapeutic doses are reported in parentheses.
[d]Data obtained with ^{14}C-loratadine.

up to 30 mg (sixfold the recommended dose) was demonstrated in a formal TQT study.[21]

3.3 | Ebastine

Ebastine is a second-generation piperidine antihistamine structurally related to terfenadine whose recommended dose is 10 mg/day. After being absorbed, ebastine is almost completely converted by CYP2J2 in the liver into the active metabolite carebastine.[49] It is carebastine that is usually measured in plasma for pharmacokinetic studies.[50] In Xenopus oocytes, ebastine blocked heterologously expressed hERG channels with a similar affinity (Kd = 300 vs 400 nM) but with lesser efficacy (46% vs 80%) than terfenadine.[51] No data are available on the effect of the active metabolite carebastine on recombinant hERG, but Moss and Morganroth[52] mention a personal communication by Roy and Brown stating that, unlike ebastine, this molecule is inactive. Carebastine shows almost linear kinetics with C_{max} values linearly related to the dose when single ebastine doses of 10, 30, 40, 50 and 90 mg are used.[53] Data obtained in human studies suggest a good cardiovascular tolerability of ebastine even when updosed. Indeed, when Moss et al[54] performed a pooled analysis of the ECG findings obtained in the preapproval clinical trials with ebastine, they found no QTc prolongation at the doses of 10 and 20 mg but slight and non-clinically relevant QTc interval increase when given at doses of 60 and 100 mg/day.[55]

3.4 | Fexofenadine

Fexofenadine is the active carboxylated metabolite of terfenadine that is generated in vivo by CYP3A4-dependent oxidative N-dealkylation.[56] The recommended dose of fexofenadine is 180 mg orally once a day or 60 mg orally 2 times a day. No cardiotoxicity is expected when updosing fexofenadine because the peak concentrations attained even after the administration of high doses of the drug are more than tenfold lower than the IC_{50} for human hERG channels (Table 1).[57] More specifically, Russel et al[58] found that the fexofenadine C_{max} was at least 20 times lower than hERG IC_{50} after the administration of a single dose of 800 mg (4.4 fold higher than the recommended dose of 180 mg/day) or after the repeated administration of 690 mg twice daily (about 8 fold higher than the recommended dose of 180 mg/day). Pratt et al[59] performed a pooled retrospective analysis of the data on cardiovascular safety collected during the clinical trials with fexofenadine (in doses up to 800 mg once daily or 690 mg twice daily) in healthy subjects and patients with seasonal allergic rhinitis. Overall more than 2100 ECGs and approximately 6000 clinical histories were reviewed with no evidence, respectively, of QT prolongation and cardiac toxicity even at the highest fexofenadine doses.[59] In addition, fexofenadine doses up to 240 and 540 mg/day were used in studies on urticaria in Japan[60] and India,[37] respectively, without any significant unwanted cardiac effect.

3.5 | Loratadine and desloratadine

Loratadine is a second-generation piperidine antihistamine drug structurally related to azatadine and cyproheptadine.[61] Loratadine is very well tolerated because it lacks anticholinergic activity and does not cross the blood-brain barrier to cause sedation.[62] After oral administration, this drug undergoes extensive first pass metabolism being converted by CYP3A4 and CYP2D6 to its active metabolite descarboethoxyloratadine (desloratadine), which is about four times more potent at H_1 receptors than loratadine itself.[62,63] Desloratadine has been developed as a drug with clinical indications similar to those of loratadine but with higher potency, longer half-life and lower binding to plasma proteins.[64,65] The recommended doses of loratadine and desloratadine are 10 and 5 mg/day, respectively. Both drugs have been used in several studies at higher than standard doses, including some in patients with urticaria.[36,40,66-72] Updosing of loratadine and desloratadine to up to fourfold the standard dose does not impose a significant risk of arrhythmias. Loratadine and desloratadine block cloned hERG channels in mammalian cells with much lower potency than terfenadine (330 nM), with estimated IC_{50} values of about 5000-100000 nM for the former and 1950 nM for the latter.[44,45,73,74] These IC_{50} values are more than 300 times higher than the maximal plasma concentration attained by loratadine and desloratadine after a single administration of the recommended daily doses of 10 and 5 mg, respectively.[75-77] Importantly, C_{max} values were more than 100 times lower than hERG IC_{50} values when loratadine or desloratadine was updosed twofold or fourfold[75-77] (Table 1). Likewise, during the repeated administration of recommended, double and fourfold doses of loratadine, C_{max} was almost a hundred times lower than hERG IC_{50} at steady state (Table 1).[75] Collectively, these data point to remarkable cardiovascular safety of both loratadine and desloratadine even when updosed as also confirmed in clinical trials in humans that were performed by a non-TQT approach before the ICH E4 guideline approval. Specifically, no significant effect on cardiac repolarization was observed with loratadine at the recommended dose of 10 mg,[78-81] when given for two weeks at a twofold higher dose,[82] or when used for 13 weeks at a fourfold higher dose.[83] Also, desloratadine did not prolong QTc when given at the recommended 5 mg daily dose[84] or at the dose of 7.5 mg/day.[85,86] No published data are available for higher desloratadine doses with the only exception of an abstract showing the lack of any significant prolongation of QTc after the administration for 10 days at doses ninefold higher than those recommended.[87]

3.6 | Mizolastine

The recommended dose of the piperidine sgAH mizolastine is 10 mg. Mizolastine blocks hERG channels with an IC_{50} of 3400 nM in Xenopus oocytes and of 350 nM in mammalian cells.[88] The C_{max} of mizolastine was 527 nM after the administration of a single 10 mg dose and 2268 nM when a 40 mg single dose was given.[89] At steady state, after the repeated administration of 10 and 40 mg daily doses for 7 days, C_{max} values, respectively, of 539 and 2446 nM were obtained.[89] Though these values are close to the IC_{50} for hERG blockade, the free concentration of mizolastine that is actually available to interact with cardiac hERG channels is much lower (around 10 nM) because of the high binding to plasma proteins.[90] The cardiovascular safety of mizolastine in doses higher than those recommended was investigated in two non-TQT studies. In the first of these studies, Chaufour et al.[89] measured the effect on QTc of 10, 20 and 40 mg mizolastine given as single or repeated daily doses for 7 days, without any significant change in ventricular repolarization. Similar results were obtained in the second study, by Delauche-Cavallier et al.,[91] who tested the effect of mizolastine up to 75 mg single dose and 40 mg repeated dose, again without any drug-induced QTc prolongation. Therefore, available evidence suggests that mizolastine can be safely updosed fourfold without inducing any significant change in cardiac risk.

3.7 | Rupatadine

Rupatadine is a sgAH of the piperidine subfamily which differs from other sgAHs in its ability to also block PAF receptors.[92,93] The recommended dosage of rupatadine is 10 mg once a day. Studies in vitro showed that rupatadine blocks hERG channels with a IC_{50} of 8100 nM.[94] As previously reported also, the hERG IC_{50} of desloratadine, the major metabolite generated by rupatadine in vivo, is in the μM range. After oral administration of single or of repeated (five days) standard 10 mg dose doses, rupatadine C_{max} was always about 2000-fold lower than the aforementioned average IC_{50} for hERG blockade (Table 1).[95,96] Church and colleagues[2] showed that after a single dose of 40 mg (fourfold higher than the recommended dose),

rupatadine C_{max} was 36.38 nM, whereas Taubel et al.[96] found values of 38.5 and 552.9 nM in Caucasian subjects receiving 100 mg rupatadine (ten times the recommended dose) as a single or as repeated doses, respectively. An ICH-compliant TQT study showed that rupatadine at a dose of 100 mg, tenfold higher than the recommended dose, did not induce significant changes in cardiac repolarization neither when given as a single dose nor when administered once a day for 5 days.[19] Similar results have recently been reported in Japanese volunteers by Taubel et al.[96] In conclusion, rupatadine updosing does not seem to increase the length of cardiac repolarization to any extent.

4 | CONCLUSIONS

As stated in the introduction, the first-line treatment of patients with CSU is the use of standard dosed non-sedating second-generation H_1 antihistamines.[1] However, many patients with CSU do not show complete control of their disease with standard doses.[97] In these patients, updosing of up to fourfold higher than standard doses of their H_1 antihistamine is recommended by the current EAACI/GA^{2}LEN/EDF/WAO guideline for urticaria.[1] Several studies have confirmed that treatment of CSU by higher than standard doses of H_1 antihistamine, that is updosing of an sgAH, is more effective than treatment with the standard dose for most sgAHs.[27,36,38,72,98,99] No cardiotoxicity was reported in any of these studies. In contrast to updosing, one study has shown that the use of a combination of H_1 antihistamines each at their licensed dose is less effective than updosing with a single antihistamine.[100] The authors suggest that the reason for this is unknown interactions and addition of side-effects in the combination therapy.

Despite the clear guidelines and the overwhelming evidence of the clinical benefit of updosing, a recent survey of 528 patients with uncontrolled CSU and who were eligible for treatment escalation showed that only 3% received up dosing of H_1 antihistamines.[101] The reasons for this are not well understood but are held to include that updosing is off-label and perceived to be linked to reduced cardiac safety.

Our present review clearly shows that sgAHs, at up to fourfold their standard dose, have excellent cardiac safety profiles, although there are differences in the quality of the supporting evidence for the safety of the different drugs. However, lower quality evidence does not mean lower cardiac safety. A review by Olasińska-Wiśniewska[102] supports our findings and concludes that such phenomena are potentially manifested only in the cases of high overdose far beyond the suggested therapeutic levels. A potential limitation of our study, however, is that the data that we reviewed were mainly obtained either in studies in vitro or in healthy volunteers. Therefore, we cannot exclude that some difference could exist in patients affected with chronic urticaria. Furthermore, there are certain groups of patients, especially the ones with inherited long QT syndrome, the elderly (ie according to WHO definitions, people older than 65 years[103]) and patients with cardiovascular diseases, who require special attention. These patients should be warned not to overdose their prescribed antihistamines and not to combine them with drugs such as antifungal drugs and macrolides, or food and beverages, such as grapefruit juice, that inhibit their metabolism by CYPs (mainly but not exclusively CYP3A4), nor with any drugs that prolong QT intervals, such as anti-arrhythmics, antimicrobials, tricyclic antidepressants, neuroleptics and prokinectics. A special caution is also advised in the presence of electrolyte unbalances such as hypokalemia and hypomagnesemia, and it should be remembered that these conditions can be precipitated by proton pumps inhibitors, drugs that, in clinical practice, are usually considered harmless.[104]

Our conclusion is that the sgAHs discussed in this review, namely bilastine, cetirizine, levocetirizine, ebastine, fexofenadine, loratadine, desloratadine, mizolastine and rupatadine, all have an excellent safety profile with no evidence of cardiotoxicity even at up to four times their standard licensed dose.

CONFLICT OF INTEREST

Mauro Cataldi has no conflict of interest to disclose. Marcus Maurer is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Aralez, Genentech, GSK, Menarini, Merckle Recordati, Moxie, Novartis, Sanofi, MSD and Uriach. Maurizio Taglialatela has no conflict of interest to disclose. Martin Church has been a speaker or consultant for Almirall, FAES Pharma, Menarini, Moxie, MSD, Novartis, UCB Pharma, Sanofi-Aventis and Uriach.

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